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INSTRUCTION
for medical use of the medicinal product

GEMCITABINE MEDAC

Composition:
active substance: gemcitabine (as gemcitabine hydrochloride);
1 ml of the reconstituted solution for infusion contains 38 mg of Gemcitabine medac (as gemcitabine hydrochloride).
excipients: mannitol (E 421), sodium acetate trihydrate, hydrochloric acid, sodium hydroxide.

Pharmaceitical form. Powder for solution for infusion.
Basic physical and chemical properties: white or off-white powder.

Pharmacotherapeutic group.
Antineoplastic agents. Structural pyrimidine analogues. ATC code: L01B C05.

Pharmacological properties.
Pharmacodynamics.
Cytotoxic activity in cell cultures.
Gemcitabine shows significant cytotoxic effects against a variety of cultured murine and human tumour cells. Its action is phase-specific such that gemcitabine primarily kills cells that are undergoing DNA synthesis (S-phase) and, under certain circumstances, blocks the progression of cells at the junction of the G1/S phase boundary. *In vitro*, the cytotoxic effect of gemcitabine is dependent on both concentration and time.
Mechanism of action.
Cellular metabolism and mechanism of action.
Gemcitabine (dFdC) is a pyrimidine antimetabolite which is metabolised intracellularly by nucleoside kinase to the active diphosphate (dFdCDP) and triphosphate (dFdCTP) nucleosides. The cytotoxic effect of gemcitabine is due to inhibition of DNA synthesis by two mechanisms of action by dFdCDP and dFdCTP. First, dFdCDP inhibits ribonucleotide reductase which is uniquely responsible for catalysing the reactions that produce deoxynucleoside triphosphates (dCTP) for DNA synthesis. Inhibition of this enzyme by dFdCDP reduces the concentration of deoxynucleosides in general and, in particular, dCTP. Second, dFdCTP competes with dCTP for incorporation into DNA (self-potentiation).
Likewise, a small amount of gemcitabine may also be incorporated into RNA. Thus, the reduced intracellular concentration of dCTP potentiates the incorporation of dFdCTP into DNA. DNA polymerase epsilon lacks the ability to eliminate gemcitabine and to repair the growing DNA strands. After gemcitabine is incorporated into DNA, one additional nucleotide is added to the growing DNA

strands. It leads to a complete inhibition in further DNA synthesis (masked chain termination) and programmed cell death process known as apoptosis.

Pharmacokinetics.
Plasma concentrations of the parent compound following a dose of 1,000 mg/m^2/30 minutes are greater than 5 µg/ml for approximately 30 minutes after the end of the infusion, and greater than 0.4 µg/ml for an additional hour.
Distribution.
The volume of distribution of the central compartment was 12.4 l/m^2 for women and 17.5 l/m^2 for men (inter-individual variability was 91.9%). The volume of distribution of the peripheral compartment was 47.4 l/m^2 and was not sensitive to gender. The plasma protein binding was considered to be negligible.
Half-life.
This period is ranged from 42 to 94 minutes depending on age and gender. For the recommended dosing schedule, Gemcitabine elimination should be virtually complete within 5 to 11 hours of the start of the infusion. Gemcitabine does not accumulate when administered once weekly.
Metabolism.
Gemcitabine is rapidly metabolised by cytidine deaminase in the liver, kidney, blood and other tissues. Intracellular metabolism of gemcitabine produces the gemcitabine mono-, di- and triphosphates (dFdCMP, dFdCDP and dFdCTP) of which dFdCDP and dFdCTP are considered active. These intracellular metabolites have not been detected in plasma or urine. The primary metabolite, 2'-deoxy-2', 2'-difluorouridine (dFdU), is not active and is found in plasma and urine.
Excretion.
Systemic clearance ranged from 29.2 l/hr/m^2 to 92.2 l/hr/m^2 depending on gender and age (inter-individual variability was 52.2%). Clearance for women is approximately 25% lower than the values for men. Although rapid, clearance for both men and women appears to decrease with age. For the recommended gemcitabine dose of 1,000 mg/m^2 given as a 30-minute infusion, lower clearance values for women and men should not necessitate a decrease in the gemcitabine dose.
Urinary excretion: Less than 10% is excreted as unchanged drug.
Renal clearance was 2 to 7 l/hr/m^2.
During the week following administration, 92 to 98% of the dose administered is recovered, 99% in the urine, mainly in the form of dFdU and 1% of the dose is excreted in faeces.
Gemcitabine medac and paclitaxel combination therapy.
Combination therapy did not alter the pharmacokinetics of either gemcitabine or paclitaxel.
Gemcitabine medac and carboplatin combination therapy.
When given in combination with carboplatin the pharmacokinetics of gemcitabine was not altered.
Renal impairment.
Mild to moderate renal insufficiency (GFR from 30 ml/min to 80 ml/min) has no consistent, significant effect on gemcitabine pharmacokinetics.

Clinical characteristics.
Indications.
Biliary duct cancer.
Gemcitabine medac is indicated for the treatment of patients with biliary duct cancer.
Bladder cancer. Gemcitabine medac in combination with cisplatin is indicated for treatment of locally recurrent or metastatic bladder cancer.
Breast cancer. Gemcitabine medac in combination with paclitaxel is indicated for treatment of patients with unresectable, locally recurrent or metastatic breast cancer after the adjuvant/neoadjuvant chemotherapy. Prior to the chemotherapy, treatment with anthracycline is recommended (if not contra-indicated).
Non-small cell lung cancer. Gemcitabine medac in combination with cisplatin is recommended as first-line drug for with locally recurrent or metastatic non-small cell lung cancer. Gemcitabine medac as monotherapy is indicated for elderly patients and patients with performance status 2.

Ovarian cancer. Gemcitabine medac in combination with Carboplatin is indicated for patients with locally recurrent or metastatic epithelial ovarian carcinoma. Gemcitabine medac is indicated for patients with a relapse of epithelial ovarian carcinoma following a period of remission (remission duration ≥ 6 months) after prior therapy with platinum-based drugs (as first-line drugs).
Pancreatic cancer. Gemcitabine medac is indicated for patients with locally recurrent or metastatic adenocarcinoma of the pancreas.

Contraindications.
Hypersensitivity to the active substance or to any of the excipients.
Breast feeding.

Special precautions for use.
Peculiarities of infusion solution preparation.
As Gemcitabine medac is a cytotoxic drug, special precautions should be taken when preparing and administering the solution for infusion. The preparation of injectable solutions of cytotoxic agents is to be carried out in a designated area. Disposable gloves and protective coats should be worn. If it is impossible to work in a designated area, face mask and suitable eye protection should be worn.
The solutions can cause serious eye irritation. If accidental contamination occurs, the eye should be washed with water thoroughly and immediately. If the irritation persists, a consultation of an eye specialist is recommended. If the solution comes into contact with skin, the skin should be washed with water immediately.

Interaction with other medicinal products and other forms of interactions.
No related studies have been conducted.
Radiotherapy.
Concurrent radiotherapy (given together or ≤ 7 days apart). Toxicity associated with this multimodality therapy is dependent on many different factors, including dose of Gemcitabine medac, frequency of Gemcitabine medac administration, dose of radiation, radiotherapy planning technique, the target tissue, and target volume.
Pre-clinical and clinical studies have shown that Gemcitabine medac has radiosensitising activity. In a single trial, where Gemcitabine medac at a dose of 1,000 mg/m^2 was administered concurrently for up to 6 consecutive weeks with therapeutic thoracic radiation to patients with non-small cell lung cancer, significant toxicity in the form of severe, and potentially life threatening mucositis, especially oesophagitis, and pneumonitis was observed, particularly in patients receiving large volumes of radiotherapy [median treatment volumes 4,795 cm^3]. During the following investigations there was proposed a rational possibility to administer Gemcitabine medac in lower doses with a concurrent radiotherapy with an expected toxicity, as it was done in Phase II non-small cell lung cancer where irradiation of the chest in the dose of 66 Gy was used together with Gemcitabine medac administration (600 mg/m^2, four times) and cisplatin (80 mg/m^2, two times) during 6 weeks. The optimum regimen for safe administration of Gemcitabine medac with therapeutic doses of radiation has not yet been determined in all tumour types.
Non-concurrent (given >7 days apart). Analysis of the data does not indicate any enhanced toxicity when Gemcitabine medac is administered more than 7 days before or after radiation, other than radiation recall. Data suggest that Gemcitabine medac can be started after the acute effects of radiation have resolved or at least one week after radiation.
Radiation injury has been reported on targeted tissues (e.g. oesophagitis, colitis, and pneumonitis) in association with both concurrent and non-concurrent use of Gemcitabine medac.
Others.
Co-using of yellow fever and other live attenuated vaccines are not recommended, due to the risk of systemic, possibly fatal disease, particularly in immunosuppressed patients.

Special precautions.

Prolongation of the infusion time and increased dosing frequency have been shown to increase toxicity.
Haematological toxicity.
Gemcitabine medac can suppress bone marrow function as manifested by leukopenia, thrombocytopenia and anaemia.
Patients receiving Gemcitabine medac should be monitored prior to each dose for platelet, leukocyte and granulocyte counts. Suspension or modification of therapy should be considered when drug-induced bone marrow depression is detected. However, myelosuppression is short lived and usually does not result in dose reduction and rarely in discontinuation.
Peripheral blood counts may continue to deteriorate after Gemcitabine medac administration has been stopped. In patients with impaired bone marrow function, the treatment should be started with caution. As with other cytotoxic treatments, the risk of cumulative bone-marrow suppression must be considered when Gemcitabine medac treatment is given together with other chemotherapy.
Hepatic insufficiency. Gemcitabine medac should be used with caution in patients with hepatic insufficiency or with impaired renal function as there is insufficient information from clinical studies to allow clear dose recommendation for this patient population. Administration of Gemcitabine medac in patients with concurrent liver metastases or a pre-existing medical history of hepatitis, alcoholism or liver cirrhosis may lead to exacerbation of the underlying hepatic insufficiency. Laboratory evaluation of renal and hepatic function (including virological tests) should be performed periodically.
Concomitant radiotherapy.
During concomitant radiotherapy (given together or ≤ 7 days apart) toxicity has been reported.
Live vaccinations.
Yellow fever vaccine and other live attenuated vaccines are not recommended in patients treated with Gemcitabine medac.
Posterior reversible encephalopathy syndrome.
Reports of posterior reversible encephalopathy syndrome (PRES) with potentially severe consequences have been reported in patients receiving Gemcitabine medac as single agent or in combination with other chemotherapeutic agents. Acute hypertension and seizure activity were reported in most Gemcitabine medac patients experiencing PRES, but other symptoms such as headache, lethargy, confusion and blindness could also be present.
Diagnosis is optimally confirmed by magnetic resonance imaging (MRI). PRES was typically reversible with appropriate supportive measures. Gemcitabine medac should be permanently discontinued and supportive measures implemented, including blood pressure control and anti-seizure therapy, if PRES develops during therapy.
Cardiovascular system.
Due to the risk of cardiac and/or vascular disorders with Gemcitabine medac, particular caution must be exercised with patients presenting a history of cardiovascular events.
"Capillary leak syndrome".
"Capillary leak syndrome" has been reported in patients receiving Gemcitabine medac as single agent or in combination with other chemotherapeutic agents. The condition is usually treatable if recognized early and managed appropriately, but fatal cases have been reported. The condition involves systematic capillary hyperpermeability during which fluid and proteins from the intravascular space leak into the interstitum. The clinical features include generalized oedema, weight gain, hypoalbuminaemia, severe hypotension, acute renal imparment and pulmonary oedema. Gemcitabine medac should be discontinued and supportive measures implemented if "capillary leak syndrome" develops during therapy. "Capillary leak syndrome" can occur in later cycles and has been associated in the literature with adult respiratory distress syndrome.
Pulmonary system.
Pulmonary effects, sometimes severe (such as pulmonary oedema, interstitial pneumonitis or adult respiratory distress syndrome [ARDS]) have been reported in association with Gemcitabine medac therapy. The aetiology of these effects is unknown. If such effects develop, consideration should be made to discontinuing Gemcitabine medac therapy. Early use of supportive care measure may help ameliorate the condition.

Renal and urogenital system.
Haemolytic uremic syndrome (HUS)
Clinical findings consistent with the haemolytic uremic syndrome (HUS) were rarely reported in patients receiving Gemcitabine medac.
Gemcitabine medac should be discontinued at the first signs of any evidence of microangiopathic haemolytic anaemia, such as rapidly falling haemoglobin with concomitant thrombocytopenia, elevation of serum bilirubin, serum creatinine, blood urea nitrogen, or LDH. Renal failure may not be reversible with discontinuation of therapy and dialysis may be required.
Fertility.
In fertility studies Gemcitabine medac caused hypospermatogenesis in male mice. Therefore, men being treated with Gemcitabine medac are advised not to father a child during and up to 6 months after treatment and to seek further advice regarding cryoconservation of sperm prior to treatment because of the possibility of infertility due to therapy with Gemcitabine medac.
Sodium.
The 200 mg vial of Gemcitabine medac contains 3.5 mg (< 1 mmol) sodium per vial.
The 1000 mg vial of Gemcitabine medac contains 17.5 mg (< 1 mmol) sodium per vial.
The 1500 mg vial of Gemcitabine medac contains 26.3 mg (> 1 mmol) sodium per vial.
This should be taken into consideration by patients on a controlled sodium diet.

Use in pregnancy and lactation period.
Pregnancy.
There are no adequate data from the use of Gemcitabine medac in pregnant women. Studies in animals have shown reproductive toxicity. Based on results from animal studies and the mechanism of action of Gemcitabine medac, this substance should not be used during pregnancy unless clearly necessary. Women should be advised not to become pregnant during treatment with Gemcitabine medac and to warn their attending physician immediately, should this occur after all.
Breast-feeding.
It is not known whether Gemcitabine medac is excreted in human milk and adverse effects on the suckling child cannot be excluded. Breast-feeding should be discontinued during treatment with Gemcitabine medac.
Fertility.
In fertility studies Gemcitabine medac caused hypospermatogenesis in male mice. Therefore, men being treated with Gemcitabine medac are advised not to father a child during and up to 6 months after treatment and to seek further advice regarding cryoconservation of sperm prior to treatment because of the possibility of infertility due to therapy with Gemcitabine medac.

Effects on ability to drive and use machines.
No studies on the effects on the ability to drive and use machines have been performed. However, Gemcitabine medac has been reported to cause mild to moderate somnolence, especially in combination with alcohol consumption. Patients should be cautioned against driving or operating machinery until it is established that they do not become somnolent.

Posology and method of administration.
Gemcitabine medac should only be prescribed by a physician qualified in the use of anti-cancer chemotherapy.
Posology.
Biliary duct cancer.
Monotherapy. For adults: the recommended dose of Gemcitabine medac is 1000 mg/m^2, given by 30-minute intravenous infusion. This should be repeated once weekly for 3 weeks, followed by a 1-week rest period. This 4-week cycle is then repeated. Dosage reduction with each cycle or within a cycle may

be applied based upon the grade of toxicity experienced by the patient.
Combination use. For adults: Gemcitabine medac in combination with cisplatin: it is recommended to use cisplatin 70 mg/m^2 on Day 1 of the cycle as an intravenous infusion, then the dose of Gemcitabine medac of 1250 mg/m^2. Gemcitabine medac should be administered on Days 1 and 8 of each 21-day cycle, as a 30-minute intravenous infusion.
This 3-week cycle is then repeated. Dosage reduction with each cycle or within a cycle may be applied based upon the grade of toxicity experienced by the patient.
Bladder cancer.
Combination use. For adults: the recommended dose of Gemcitabine medac is 1000 mg/m^2, given by a 30-minute intravenous infusion. This dose should be administered on Days 1, 8 and 15 of each 28-day cycle in combination with cisplatin. It is recommended to use cisplatin 70 mg/m^2 on Day 1 after Gemcitabine medac or on Day 2 of each 28-day cycle.
This 4-week cycle is then repeated. Dosage reduction with each cycle or within a cycle may be applied based upon the grade of toxicity experienced by the patient.
Breast cancer
Combination use. For adults: Gemcitabine medac in combination with paclitaxel is recommended in the following regimen: paclitaxel (175 mg/m^2) administered on Day 1 over approximately 3-hours as an intravenous infusion, followed by Gemcitabine medac (1250 mg/m^2) as a 30-minute intravenous infusion on Days 1 and 8 of each 21-day cycle. Dose reduction with each cycle or within a cycle may be applied based upon the grade of toxicity experienced by the patient. Patients should have an absolute granulocyte count of at least 1500 (x 10^6/l) prior to initiation of Gemcitabine medac + paclitaxel combination.
Non-small cell lung cancer.
Monotherapy. For elderly age: the recommended dose of Gemcitabine medac is 1000 mg/m^2, given by 30-minute intravenous infusion. This should be repeated once weekly for 3 weeks, followed by a 1-week rest period. This 4-week cycle is then repeated. Dosage reduction with each cycle or within a cycle may be applied based upon the grade of toxicity experienced by the patient.
Combination use. For adults: the recommended dose for Gemcitabine medac is 1250 mg/m^2 body surface area given as a 30-minute intravenous infusion on Day 1 and 8 of the treatment cycle (21 days). Dosage reduction with each cycle or within a cycle may be applied based upon the grade of toxicity experienced by the patient. Cisplatin has been used at doses between 75-100 mg/m^2 once every 3 weeks.
Ovarian cancer.
Combination use. For adults: Gemcitabine medac in combination with carboplatin is recommended using Gemcitabine medac 1000 mg/m^2 administered on Days 1 and 8 of each 21-day cycle as a 30-minute intravenous infusion. After Gemcitabine medac, carboplatin will be given on Day 1 consistent with a target Area under curve (AUC) of 4.0 mg/ml·min. Dosage reduction with each cycle or within a cycle may be applied based upon the grade of toxicity experienced by the patient.
Pancreas cancer.
For adults: The recommended dosage of Gemcitabine medac for adults is 1000 mg/ ^{2} as a 30-minute intravenous infusion. The infusion should be given once a week seven weeks in a row followed by a one-week rest period. This 3-week cycle is then repeated with a break every 4th week. Dose reduction with each cycle or within a cycle may be applied based upon the grade of toxicity experienced by the patient.
Dose modification due to non-haematological toxicity.
Periodic physical examination and checks of renal and hepatic function should be made to detect non-haematological toxicity. Dosage reduction with each cycle or within a cycle may be applied based upon the grade of toxicity experienced by the patient.
In general, for severe (Grade 3 or 4) non-haematological toxicity, except nausea/vomiting, therapy with Gemcitabine medac should be withheld or decreased depending on the judgement of the treating physician. Doses should be withheld until toxicity has resolved in the opinion of the physician.

Dose modification due to haematological toxicity.

Initiation of a cycle.

For all indications, the patient must be monitored before each dose for platelet and granulocyte counts. Patients should have an absolute granulocyte count of at least 1500 (x 10^6/l) and platelet account of 100000 (x 10^6/l) prior to the initiation of a cycle.

Within a cycle.

Dose modifications of Gemcitabine medac within a cycle should be performed according to the following tables:

Dose modification of Gemcitabine medac within a cycle for bladder cancer, NSCLC and pancreatic cancer, given in monotherapy or in combination with cisplatin			
Absolute granulocyte count (x 10^6/l)		Platelet count (x 10^6/l)	Percentage of standard dose of Gemcitabine medac (%)
> 1000	and	> 100000	100
500-1000	or	50000-100000	75
<500	or	< 50000	Omit dose *

*Treatment omitted will not be re-instated within a cycle before the absolute granulocyte count reaches at least 500 (x10^6/l) and the platelet count reaches 50000 (x10^6/l).

Dose modification of Gemcitabine medac within a cycle for breast cancer, given in combination with paclitaxel			
Absolute granulocyte count (x 10^6/l)		Platelet count (x 10^6/l)	Percentage of standard dose of Gemcitabine medac (%)
≥ 1200	and	>75000	100
1000- <1200	or	50000-75000	75
700- <1000	and	≥ 50000	50
<700	or	<50000	Omit dose*

*Treatment omitted will not be re-instated within a cycle. Treatment will start on day 1 of the next cycle once the absolute granulocyte count reaches at least 1500 (x10^6/l) and the platelet count reaches 100000 (x10^6/l).

Dose modification of Gemcitabine medac within a cycle for ovarian cancer, given in combination with carboplatin			
Absolute granulocyte count (x 10^6/l)		Platelet count (x 10^6/l)	Percentage of standard dose of Gemcitabine medac (%)
> 1500	and	≥ 100000	100
1000-1500	or	75000-100000	50
<1000	or	< 75000	Omit dose*

*Treatment omitted will not be re-instated within a cycle. Treatment will start on day 1 of the next cycle once the absolute granulocyte count reaches at least 1500 (x10^6/l) and the platelet count reaches 100000 (x10^6/l).

Dose modifications due to haematological toxicity in subsequent cycles, for all indications.
The Gemcitabine medac dose should be reduced to 75% of the original cycle initiation dose, in the case of the following haematological toxicities:

- Absolute granulocyte count < 500 x 10^6/l for more than 5 days
- Absolute granulocyte count < 100 x 10^6/l for more than 3 days
- Febrile neutropenia
- Platelets < 25 000 x 10^6/l
- Cycle delay of more than 1 week, due to toxicity.

Method of administration.
Gemcitabine medac is tolerated well during infusion and may be administered ambulant. If extravasation occurs, generally the infusion must be stopped immediately and started again in another blood vessel. The patient should be monitored carefully after the infusion administration.
Special populations.
Patients with renal or hepatic impairment. Gemcitabine medac should be used with caution in patients with hepatic or renal insufficiency as there is insufficient information from clinical studies to allow for clear dose recommendations for these patient populations.
Elderly population (> 65 years). Gemcitabine medac has been well tolerated in patients over the age of 65. There is no evidence to suggest that dose adjustments, other than those already recommended for all patients, are necessary in the elderly.
Paediatric population. Not recommended for paediatric use because there is not enough sufficient data regarding the efficacy and safety of Gemcitabine medac in children.
Guidelines for reconstitution (and further dilution, if needed). Gemcitabine medac sterile powder has only been shown to be compatible with the PF sodium chloride 0,9% solution for injection.
According to the solubility indexes, maximum Gemcitabine medac concentration after the preparation of solution is 40mg/ml. Reconstitutions at concentrations greater than 38 mg/ml may result in incomplete dissolution, and should be avoided.
1. The reconstitution and the further dilution should take place in aseptic conditions.
2. To reconstitute, add not less than 5 ml of 0,9% sodium chloride solution for injection in a vial with 200 mg of Gemcitabine medac powder, or 25 ml of 0,9 % sodium chloride solution for injection in a vial with 1000 mg of Gemcitabine medac powder. The total volume after dissolution is 5,26 ml (vials with 200 mg of Gemcitabine medac) and 26,3 ml (vials with 1000 mg of Gemcitabine medac). It ensures that the concentration of Gemcitabine medac is 38 mg/ml, taking into account the volume replaced with lyophillisate. Shake to dissolve. The reconstituted product may be further diluted with PF sodium chloride 0,9% solution for injection. The color of the solution may vary from transparent to light yellow
3. Parenteral medicinal products should be inspected visually for particulate matter and discoloration. If the product includes any foreign particles, it should not be used. Any unused parts of the medicinal product should be discarded according to the legislation.

Paediatric population.
Study data is limited to establish the efficacy and safety of Gemcitabine medac in children.

Overdose.
Symptoms: Doses as high as 5,7g/m^2 have been administered by intravenous infusion over 30-minutes every 2 weeks with clinically acceptable toxicity.
Treatment: In the event of suspected overdose, the patient should be monitored with appropriate blood counts and receive supportive therapy, as necessary. There is no known antidote for overdose of gemcitabine.

Undesirable effects.
The most commonly reported adverse drug reactions associated with Gemcitabine medac treatment include: nausea with or without vomiting, raised liver transaminases (AST/ALT) and alkaline phosphatase, proteinuria, haematuria, dyspnoea, allergic skin rashes.

The frequency and severity of the adverse reactions are affected by the dose, infusion rate and intervals between doses. Dose-limiting adverse reactions are reductions in thrombocyte, leukocyte and granulocyte counts.
Given list with adverse reactions and frequency is received in clinical investigations. The adverse reactions in each group is given in order of reducing the severity and frequency: very common (≥1/10), common (≥1/100 and <1/10), uncommon (≥1/1000 and <1/100), rare (≥1/10000 and <1/1000), very rare (<1/10000).

System Organ Class	Frequency
Infections and infestations	Common • Infections Uncommon • Sepsis
Blood and lymphatic system disorders	Very common • Leukopenia (Neutropenia Grade 3 = 19.3 %; Grade 4 = 6 %); bone marrow suppression is usually mild to moderate and mostly affects the granulocyte count • Thrombocytopenia • Anaemia Common • Febrile neutropenia Uncommon • Thrombotic microangiopathy Very rare • Thrombocytosis
Immune system disorders	Very rare • Anaphylactoid reaction
Metabolism and nutrition disorders	Common • Anorexia
Nervous system disorders	Common • Headache • Insomnia • Somnolence Uncommon • Cerebrovascular accident Very rare • Posterior reversible encephalopathy syndrome
Cardiovascular system	Uncommon • Arrhythmias, predominantly supraventricular in nature • Heart failure Rare • Myocardial infarct

System Organ Class	Frequency
	• Clinical signs of peripheral vasculitis and gangrene • Hypotension Very rare • Capillary leak syndrome
Respiratory, thoracic and mediastinal disorders	Very common • Dyspnoea – usually mild and passes rapidly without treatment Common • Cough • Rhinitis Uncommon • Interstitial pneumonitis • Bronchospasm –usually mild and transient but may require parenteral treatment Rare • Pulmonary oedema • Adult respiratory distress syndrome
Gastrointestinal disorders	Very common • Vomiting • Nausea Common • Diarrhoea • Stomatitis and ulceration of the mouth constipation Very rare • Ischaemic colitis
Hepatobiliary disorders	Very common • Elevation of liver transaminases (AST and ALT) and alkaline phosphatase Common • Increased bilirubin Uncommon • Serious hepatotoxicity, including liver failure and death Rare • Increased gamma-glutamyl transferase (GGT)

System Organ Class	Frequency
Skin and subcutaneous tissue disorders	Very common • Allergic skin rash frequently associated with pruritus alopecia Common • Itching • Sweating Rare • Severe skin reactions, including desquamation and bullous skin eruptions • Ulceration • Vesicle and sore formation • Scaling Very rare • Toxic epidermal necrolysis • Stevens-Johnson syndrome
Musculoskeletal and connective tissue disorders	Common • Back pain • Myalgia
Renal and urinary disorders	Common • Haematuria • Mild proteinuria Uncommon • Renal failure • Haemolytic uraemic syndrome
General disorders	Very common • Influenza-like symptoms - the most common symptoms are fever, headache, chills, myalgia, asthenia and anorexia. Cough, rhinitis, malaise, perspiration and sleeping difficulties have also been reported. • Oedema/peripheral oedema - including facial oedema. Oedema is usually reversible after stopping treatment Common • Fever • Asthenia • Chills Rare • Injection site reactions - mainly mild in nature
Injury, poisoning, and procedural complications	Rare • Radiation toxicity • Radiation recall

Combination use in breast cancer.
The frequency of grade 3 and 4 haematological toxicities, particularly neutropenia, increases when Gemcitabine medac is used in combination with paclitaxel. However, the increase in these adverse

reactions is not associated with an increased incidence of infections or haemorrhagic events. Fatigue and febrile neutropenia occur more frequently when Gemcitabine medac is used in combination with paclitaxel. Fatigue, which is not associated with anaemia, usually resolves after the first cycle.

Grade 3 and 4 Adverse Events in monotherapy with Paclitaxel versus Gemcitabine plus Paclitaxel				
	Number (%) of Patients			
	Paclitaxel monotherapy (N = 259)		Combined use of Gemcitabine with Paclitaxel (N = 262)	
	Grade 3	Grade 4	Grade 3	Grade 4
Laboratory				
Anaemia	5 (1.9)	1 (0.4)	15 (5.7)	3 (1.1)
Thrombocytopenia	0	0	14 (5.3)	1 (0.4)
Neutropenia	11 (4.2)	17 (6.6)*	82 (31.3)	45 (17.2)*
Non-laboratory				
Febrile neutropenia	3 (1.2)	0	12 (4.6)	1 (0.4)
Fatigue	3 (1.2)	1 (0.4)	15 (5.7)	2 (0.8)
Diarrhoea	5 (1.9)	0	8 (3.1)	0
Motor neuropathy	2 (0.8)	0	6 (2.3)	1 (0.4)
Sensory neuropathy	9 (3.5)	0	14 (5.3)	1 (0.4)

*Grade 4 neutropenia lasting for more than 7 days occurred in 12.6% of patients in the combination arm and 5.0% of patients in the paclitaxel arm.

Combination use in bladder cancer.

Grade 3 and 4 Adverse Events in the use of MVAC (methotrexate, vinblastine, doxorubicin, cisplatin) versus Gemcitabine medac plus Cisplatin				
	Number (%) of Patients			
	MVAC combination (N = 196)		Combined use of gemcitabine plus cisplatin (N = 200)	
	Grade 3	Grade 4	Grade 3	Grade 4
Laboratory				
Anaemia	30 (16)	4 (2)	47 (24)	7 (4)
Thrombocytopaenia	15 (8)	25 (13)	57 (29)	57 (29)
Non-laboratory				
Nausea and vomiting	37 (19)	3 (2)	44 (22)	0 (0)
Diarrhoea	15 (8)	1 (1)	6 (3)	0 (0)
Infection	19 (10)	10 (5)	4 (2)	1 (1)
Stomatitis	34 (18)	8 (4)	2 (1)	0 (0)

Combination use in ovarian cancer.

Grade 3 and 4 Adverse Events in monotherapy with Carboplatin versus Gemcitabine plus Carboplatin				
	Number (%) of Patients			
	Carboplatin (N = 174)		Combined use of gemcitabine plus carboplatin (N = 175)	
	Grade 3	Grade 4	Grade 3	Grade 4
Laboratory				
Anaemia	10 (5.7)	4 (2.3)	39 (22.3)	9 (5.1)
Neutropaenia	19 (10.9)	2 (1.1)	73 (41.7)	50 (28.6)
Thrombocytopaenia	18 (10.3)	2 (1.1)	53 (30.3)	8 (4.6)
Leukocytopenia	11 (6.3)	1 (0.6)	84 (48.0)	9 (5.1)
Non-laboratory				
Haemorrhage	0 (0.0)	0 (0.0)	3 (1.8)	(0.0)
Febrile neutropenia	0 (0.0)	0 (0.0)	2 (1.1)	(0.0)
Infection without neutropenia	0 (0.0)	0 (0.0)	(0.0)	1 (0.6)

Sensory neuropathy was also more frequent in the combination arm than with single agent carboplatin.
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system.

Shelf life.
5 years.

Special precautions for storage
Keep out of reach of children.
This medicinal product does not require any special storage conditions. Do not refrigerate the reconstituted solution.

Incompatibilities.
Gemcitabine medac sterile powder has only been shown to be compatible with the sodium chloride 0,9% solution for injection without preservative agents.

Package.
200 mg, 1000 mg or 1500 mg in vials (Type 1).
Each cardboard box contains 1 vial.
Vial can be covered with the protective film.

Release category.
Prescription.

Manufacturer.
Medac Gesellschaft fur klinische Spezialpraparate m.b.H.

Manufacturer's location and the address of its activity.
Theaterstrasse 6, 22880 Wedel, Germany.

Last revision date.